

# Polycystic Ovarian Syndrome

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# INTRODUCTION

- Most common cause of infertility in women
- Classic syndrome originally described by Stein and Leventhal
  - Hyperandrogenism
  - Menstrual irregularity
  - Polycystic ovaries
  - Central adiposity
- Syndrome, not a disease—multiple potential etiologies with variable clinical expression

The background features a grid of 18 green spheres arranged in 3 rows and 6 columns. The spheres have a 3D effect with highlights and shadows. The background color transitions from a dark blue on the left to a lighter green on the right.

Pathogene

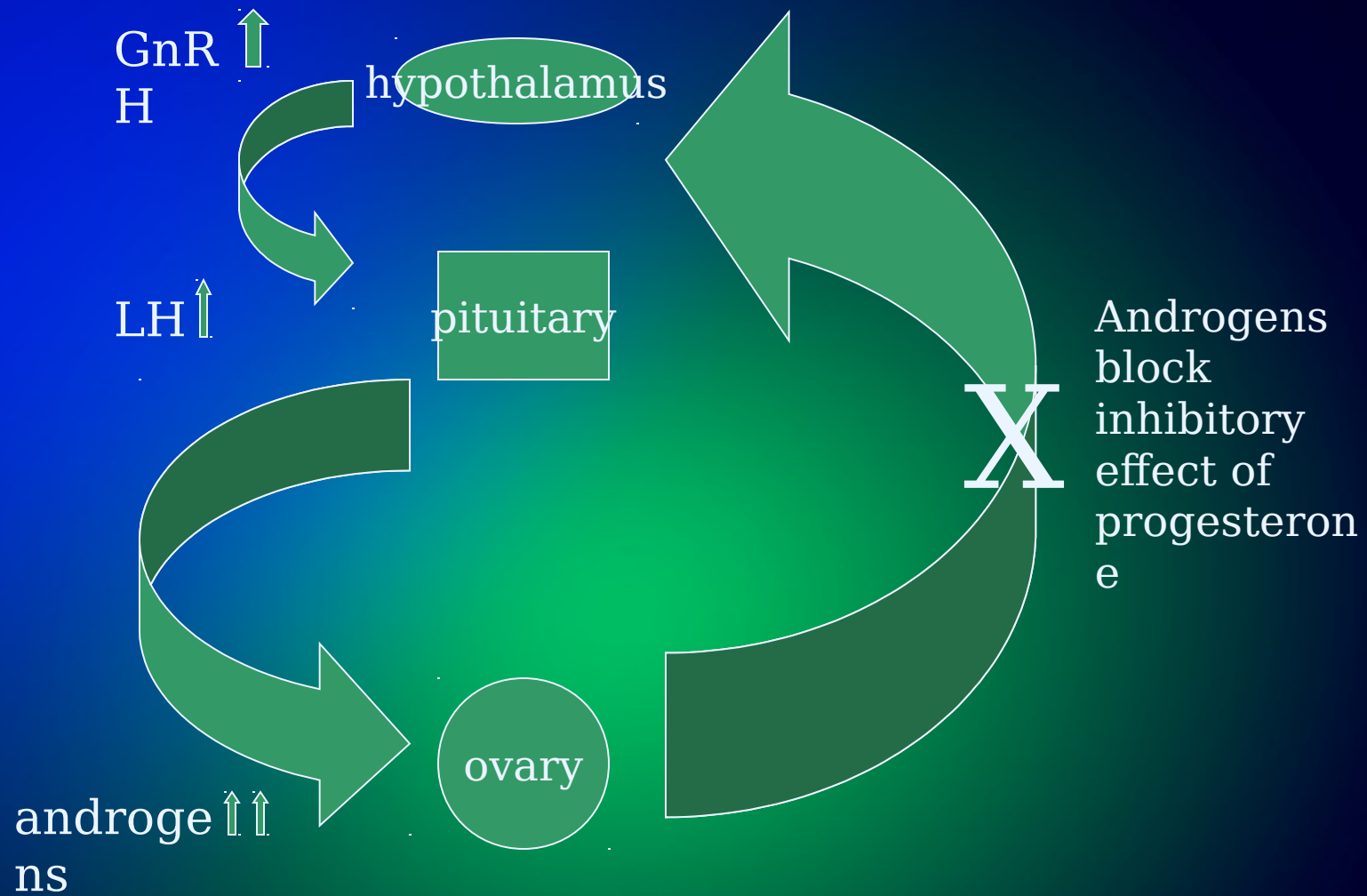
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INTRAOVARIAN  
ANDROGEN  
EXCESS

# Abnormal Pituitary Function

## —Altered Negative Feedback Loop

- Increased GnRH from hypothalamus
- Excessive LH secretion relative to FSH by pituitary gland
- LH stimulates ovarian thecal cells-- androgen production
- Ineffective suppression of the LH pulse frequency by estradiol and progesterone
- Androgen excess increases LH by blocking the hypothalamic inhibitory feedback of progesterone




# Abnormal steroidogenesis

- Intraovarian androgen excess results in excessive growth of small ovarian follicles
- Follicular maturation is inhibited
- Excess androgen causes thecal and stromal hyperplasia



# HYPERINSULINEMIA

- Excess insulin production and insulin resistance
- Genetic link
- Hyperandrogenism vs. hyperinsulinemia
  - Which came first?

The background of the slide features a grid of approximately 24 green, three-dimensional-looking spheres arranged in 4 rows and 6 columns. The spheres are set against a dark blue gradient background that transitions from a deeper blue at the top to a slightly lighter blue at the bottom. The text is centered horizontally and vertically over the grid.

# DIAGNOSTIC CRITERIA AND CLINICAL MANIFESTATIONS

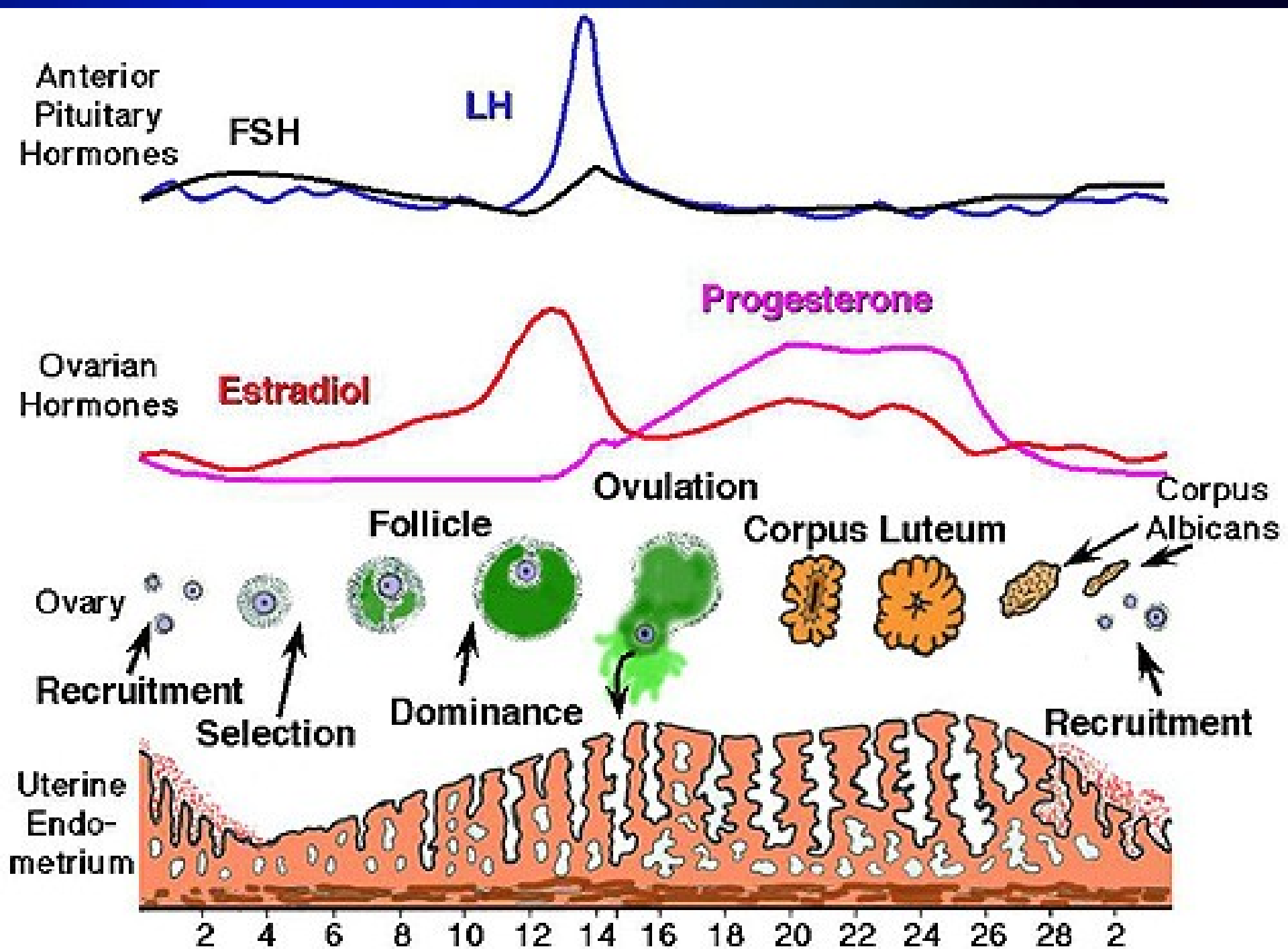


- NIH Criteria \*\*
  - Menstrual irregularity due to anovulation or oligo-ovulation
  - Evidence of clinical or biochemical hyperandrogenism
    - Hirsutism, acne, male pattern baldness
    - High serum androgen levels
  - Exclusion of other causes (CAH, tumors, hyperprolactinemia)

- Rotterdam Criteria (2 out of 3)
  - Menstrual irregularity due to anovulation oligo-ovulation
  - Evidence of clinical or biochemical hyperandrogenism
  - Polycystic ovaries by US
    - presence of 12 or more follicles in each ovary measuring 2 to 9 mm in diameter and/or increased ovarian volume

# MENSTRUAL DYSFUNCTION

- Oligo or amenorrhea
  - Menstrual irregularity typically begins in the peripubertal period
  - Delayed menarche
- Reduction in ovulatory events leads to deficient progesterone secretion
- Chronic estrogen stimulation of the endometrium with no progesterone for differentiation—intermittent breakthrough bleeding or dysfunctional uterine bleeding
- Increased risk for endometrial hyperplasia and/or endometrial CA



# HYPERANDROGENISM

- Hirsutism, acne, male pattern balding, alopecia
- 50-90% patients have elevated serum androgen levels
- Free testosterone levels most sensitive
- *Rare*: increased muscle mass, deepening voice, clitoromegaly (should prompt search for underlying neoplasm)

# OVARIAN ABNORMALITIES

- Thickened sclerotic cortex
- Multiple follicles in peripheral location
- 80% of women with PCOS have classic cysts





# INFERTILITY

- Intermittent ovulation or anovulation
- Inherent ovarian disorder—studies show reduced rate of conception despite therapy with clomid

# OBESITY

- Prevalence of obesity varies from 30-75%
- 2/3 of patients with PCOS who are not obese have excessive body fat and central adiposity
- Obese patients can be hirsute and/or have menstrual irregularities without having PCOS

# OBESITY AND INSULIN RESISTANCE

- $\frac{1}{2}$  patients with PCOS are obese
- $> 80\%$  are hyperinsulinemic and have insulin resistance (independent of obesity)
- Hyperinsulinemia contributes to **hyperandrogenism** through production in the theca cell and through its suppressive effects on sex hormone binding globulin production by the liver

# ASSOCIATED MEDICAL CONDITIONS

- Increased risk of developing Type 2 Diabetes and Gestational diabetes
- Low HDL and high triglycerides
- Sleep apnea
- Nonalcoholic steatohepatitis
- Metabolic syndrome—43% of PCOS patients (2 fold higher than age-matched population)
- Elevated CRP and heart disease
- Advanced atherosclerosis



# DIFFERENTIAL DIAGNOSIS

## 1. Hyperprolactinemia

- Prominent menstrual dysfunction
- Little hyperandrogenism

## 2. Congenital Adrenal Hyperplasia

- morning serum 17-hydroxyprogesterone concentration greater than 200 ng/dL in the early follicular phase strongly suggests the diagnosis
- confirmed by a high dose (250 mcg) ACTH stimulation test: post-ACTH serum 17-hydroxyprogesterone value less than 1000 ng/dL



### 3. Ovarian and adrenal tumors

- serum testosterone concentrations are always higher than 150 ng/dL
- adrenal tumors: serum DHEA-S concentrations higher than 800 mcg/dL
- **LOW** serum LH concentrations

### 4. Cushing's syndrome

### 5. Drugs: danazol; OCPs with high androgenicity

# TESTING

- Serum HCG
- Serum prolactin
- Thyroid panel
- FSH: r/o ovarian failure
- Serum luteinizing hormone (LH)  
—elevated
- Serum estradiol—normal
- Serum estrone—elevated

# TESTING

- Fasting glucose: elevated
- 2 hour OGTT: elevated
- Fasting insulin: elevated
- Free testosterone: elevated
- DHEA-S: normal
- 17-hydroxyprogesterone: normal
- Pelvic US
- Lipids

The background features a 3x6 grid of spheres. The spheres on the left are blue, and they gradually transition to green towards the right. The word "TREATMENT" is written in white, serif, all-caps font across the middle of the grid.

TREATMENT

# WEIGHT LOSS

- Weight loss
- Weight loss
- Weight loss

# Hirsutism

- Mechanical hair removal
- Vaniqa (eflornithine hydrochloride)
- OCPs with minimal androgenicity
- OCP plus antiandrogen (spironolactone)
- Spironolactone, 50-200 mg per day
- Flutamide
  - Potential hepatic dysfunction



# Oligomenorrhea

- Combination estrogen-progestin pill first line when fertility is not desired
  - Decrease in LH secretion and decrease in androgen production
  - Increase in hepatic production of sex-hormone binding globulin
  - Decreased bioavailability of testosterone
  - Decreased adrenal androgen secretion
  - Regular withdrawal bleeds
  - Prevention of endometrial hyperplasia

# TREATMENT—no fertility desired

- Monophasic antiandrogenic OCP
  - ON 1/35 (norethindrone)
  - Orthocyclen (norgestimate)
  - Desogen or Orthocept (desogestrel)
  - Yasmin

- Metformin

- will restore ovulation and menses in  $> 50\%$  of patients
- Treat with cyclic progestin to reduce endometrial hyperplasia if regular menses not attained
  - 10 mg for 7 to 10 days every two to four months

# METFORMIN

- Decreases hepatic glucose production
- Reduces need for insulin secretion
- Improves insulin sensitivity (increases peripheral glucose uptake and utilization)
- Antilipolytic effect—reduces fatty acid concentrations and reduces gluconeogenesis

# SIDE EFFECTS

- Diarrhea, nausea, vomiting, flatulence, indigestion, abdominal discomfort
  - Caused by lactic acid in the bowel wall
  - Minimized by slow increase in dosage
- Lactic acidosis—rare
  - Avoid in CHF, renal insufficiency, sepsis
  - Discontinue for procedures using contrast (withhold X 48 hours)
  - Temporarily suspend for all surgical procedures that involve fluid restriction
  - Cimetidine causes increased metformin levels

# INFERTILITY TREATMENT

- Metformin
  - 500 mg daily
  - Increase by 500 mg each week until:
    - Normal menses
    - Reached max dose
    - Side-effects
- Clomid
  - 50 mg days 3-7 for 3 months
  - 100 mg days 3-7 for 3 months



# METFORMIN DOSING

- Target—1500-2550 mg per day
- Clinically significant responses not regularly observed at doses less than 1000 mg per day
- Extended release formulations—fewer side-effects. Entire dose should be given with dinner

# Infertility

- Weight loss—reduction in serum testosterone concentration and resumption of ovulation
- Clomid: 80% will ovulate, 50% will conceive
- Metformin: when added to clomid, improves ovulatory rates
- FSH injections
- Laparoscopic surgery: wedge resections, laparoscopic ovarian laser electrocautery
- IVF

# Clomid Challenge Test

- Day 3 FSH and estradiol levels
- 100 mg of Clomid on cycle days 5-9
- Day 10 FSH levels
- The test is abnormal if either the day 3 or day 10 FSH values are elevated (greater than 10) or if the day 3 estradiol is greater than 80



# Questions...



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